REMARKS

In response to the final Office Action dated June 25, 2007, Applicants submit this response, an attached Expert Declaration under 37 C.F.R. § 1.132, and a Request for Continued Examination. This current application and its claims were filed, and received office actions long before the new USPTO rules come into effect on November 1, 2007, and accordingly the Request for Continued Examination should be accepted, and the claims need not be restricted to five independent twenty-five total claims.

Applicants have amended claims 1 and 111, as requested by the examiner in order to overcome the claim objections to claims stated on page two of the Office Action, and the rejection under 35 U.S.C. § 112 stated on page three of the Office Action. Support for these minor amendments can be found in the relevant claims themselves, and the terms of legal art available to all patent practitioners. After entry of the minor claim amendments offered herein, claims 1-2, 9-31, 33, 35-41, 53, 55-62, 65-71, 74-112 will be pending in the application.

REJECTIONS UNDER 35 U.S.C. § 112, 1ST PARAGRAPH

On page three of the Final Office Action, original and unamended claim 18 was newly rejected as allegedly lacking written description support under 35 U.S.C. § 112, 1st Paragraph, alleging that because of a previous amendment to claim 1, the "lipids" and "nucleic acids" listed in unamended claim 18 now lack written description support. The Office Action stated that "After the amendment to claim 1, it seems clear that the lipid of claim 18 must now come from either the dead cell in part, or the virus in whole or in part of claim 1," and that the specification does not support lipids and nucleic acids as subgenuses of dead cells in part, or the virus in whole or in part.

Applicants respectfully reply that the Examiner is mistaken on several points. First, claim 18, which has not been amended, is itself part of the specification, and hence the recitation in unamended claim 18 of lipids and nucleic acids provide their own written description support for legal purposes, at least provided lipids and nucleic acids fall within the scope of amended claim 1, which they do.

The lipids of claim 18 were originally recited as subgenera of the one or more physiologically active agents in original claim 1, and then claim 1 was amended to recite particular subgenera of physiologically active agents that include, among others, "antigens." It is well known in the art that lipids and nucleic acids can serve as antigens, and fall within the genus of antigens, and therefore fall within the scope of amended claim 1. Frankly, Applicants do not understand the purported basis for this rejection. Applicants had no legal duty whatsoever to describe in the specification particular "sources" of the lipids and nucleic acids that were recited in original claim 18, especially since both lipids and nucleic acids are available from a wide variety of "sources," both natural and un-natural. Accordingly, original claim 18 had proper written description support both before and after the amendment to claim 1, and the rejection should be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103 FOR OBVIOUSNESS

The Office Action maintained and finalized the previous rejections of all of the pending claims, as being unpatentable for obviousness under 35 U.S.C. § 103, over various references, including Baichwal (U.S. Patent No. 5,612,053), Watts (U.S. Patent No. 6,310,089), and Ni (U.S. Patent No. 5,929,051), as well as others. On pages 10-12, the Office Action rejected Applicants' previous arguments that multiple selections from the very large number of

permutations of alternative disclosures of Baichwal, Watts, Ni, and the various references to arrive at a composition "formulated as a solid mixture of components rather than a physical composite of separate ingredients, and wherein the composition is not pre-gelled as formulated, and having appropriate particle sizes wherein the particles would form a gel in situ. This is unpersuasive because it is presented as an opinion and not supported by any evidence." On page 11, the Office Action went on to allege that "It would be obvious to use the pectin of Ni in the invention of Baichwal for the reasons set forth in the rejection, and the ability to form a gel in situ would be an inherent characteristic of the resulting composition."

Applicants respectfully dispute the assertions of the Office Action. It is well know in the art that certain polysaccharides can form gels under specific conditions that typically vary widely for each specific polymer. For example, most commercially available pectins (having a high percentage of methoxyl groups) form the gels used in jellies and other food compositions at highly acidic pH, and in the presence of high concentrations of sugar, but those conditions and the formation of the resulting gels are certainly irrelevant to the *in-situ* gelling ability of a pharmaceutical composition. The Ni reference taught that the low methoxyl, high molecular weight pectins disclosed in that reference were capable of forming gels in the presence of calcium ions, but neither of Ni, Baichwal, nor any of the other references cited by the Examiner taught or suggested the preparation of pharmaceutical composition in the form of ungelled solid compositions, which would, upon application to mucosal surfaces, form a bioadhesive gel "*in-situ*," as is recited by Applicants' claims.

In order to supply evidence of the claimed composition's ability to form such "*in-situ*" gels, in the attached Declaration of inventor Yawei Ni, Ph.D., in paragraphs 12, 13, and 14,

Dr. Ni describes the preparation of examples of the claimed pharmaceutical compositions that do in fact possess the highly unique "*in-situ* gellation" property. Those compositions include a dominant percentage of an inert and highly water soluble pharmaceutical diluent and bulking agent, *i.e.*, lactose, and only very small percentages of the other water soluble ingredients, namely vaccine antigen, Aloe pectin, Povidone (polyvinyl pyrrolidone, a water soluble polymer), and water soluble buffering salts (such as sodium phosphates).

As discussed in paragraphs 14 and 16 of Dr. Ni's declaration, after their formulation into a solid mixture, these powder compositions are immediately and completely soluble in pure water, but exhibit the remarkable and unexpected property that if they are placed in aqueous simulated nasal fluids comprising about 5 milimolar Ca^{2+} salts, the particles do not dissolve, but rather immediately gel "*in-situ*"forming water insoluble gel particles and approximately double in size. Additionally, as disclosed in Figure 1 of the Ni Declaration, the formation of the "*in-situ*" gelled particles in the simulated nasal fluids results in a delayed release of vaccine antigens into the surrounding liquid medium (as measured by the HA activity of the liquid medium).

The un-gelled solid powder particles also possess another unexpected and important property as compared to liquid vaccines, namely they are thermally and storage stable, as can be seen from paragraph 15 and Table 3 of Dr. Ni's Declaration. As illustrated in Table 3, upon storage at room temperature, the HA activity of the vaccine antigens in the compositions was completely stable throughout the 24 months tested. It is worth noting that control powders having no pectin were also stable for 24 months, but the powder samples comprising the pectin had higher overall HA activity, tentatively indicating that the very small concentration of pectin

present in the solid phase apparently provided a substantial stabilization effect on the vaccine antigens.

Furthermore, if the claimed powder particle compositions (which are ungelled and soluble in pure water) are applied to the nasal mucosal surfaces of rats, they form thin gel sheets on the mucosal epithelia that persist for at least about 5 hours, as discussed in paragraph 17 and illustrated in Figure 2 of Dr. Ni's Declaration. The persistence of these highly unexpected "*in-situ*" gel sheets on the rat nasal mucosa for at least five hours stands in contrast to the well known conventional wisdom and expectations of those of ordinary skill in the drug delivery arts that the clearance time for normal materials on human nasal mucosal surfaces has been estimated to about 12-15 minutes.

Subsequent animal testing, involving application of the claimed nasal powder vaccine compositions to the nasal mucosal surfaces of rats, as described in paragraphs 19-22 and Tables 4 and 5 of Dr. Ni's Declaration, showed that inclusion of pectin in the compositions (as compared to control compositions that did not comprise the pectins) and the formation of the *in-situ* gels ultimately resulted in large increases in the immune response of the rats after one or two administrations of the powder to the nasal mucosa, *see* Tables 4 and 5.

In view of the disclosures recited above, Applicants assert that the attached Declaration of Dr. Ni, and its attachments, provide clear evidence of both the "in situ gelling" that results from the inclusion of low methoxyl, high molecular weight pectins in the compositions, and its very substantial and unexpected effects in prolonging the release of physiologically active vaccine antigens to mucosal surfaces, and a resulting unexpected increase in the immune response of the animals tested.

Applicants assert that their claimed compositions and their unexpectedly superior results in terms of thermal and storage stability, and ability to *in-situ* gel on mucosal surfaces so as to induce unexpectedly strong immune responses to the vaccine antigens meet long felt but unmet needs in the art. As discussed in paragraphs 6-10 of Dr. Ni's Declaration, and its attachments, UNICEF and the World Health Organization estimate that more than 27 million infants and 40 million pregnant women worldwide do not receive and remain in need of vaccinations.

As illustrated in Dr. Ni's Declaration, currently approved vaccine compositions are liquids that are unstable at room temperature and therefore require cold storage during manufacture and distribution. While the cold storage requirement can be readily met in many developed countries, providing refrigeration and cold storage of vaccines is a major problem in many developing countries, where breakdowns in cold storage often result in the unavailability or impaired performance of those vaccines in the field in those countries, and the unavailability and decreased acceptance of the vaccines.

Furthermore, with the exception of oral polio and a recently approved nasal liquid flu vaccine, all current vaccines are administered by injection of liquids, which results in decreased patient compliance in all countries, and risks of re-use of non-sterile needles and cross-contamination between patients is a major problem in many developing countries.

As described in Dr. Ni's Declaration, Applicants' claimed nasal powder vaccine composition meet the longfelt and unmet needs worldwide for vaccines that do not require refrigeration during distribution, and do not require administration by injection.

As a separate point, the Examiner objects on pages 11-12 of the Office Action that the ability of Applicants' claims to powder compositions that gel *in-situ*, so as overcome the

problem of rapid clearance from nasal mucosal surfaces, "does not overcome the obviousness rejection because Applicants have provided no evidence that the dry compositions of Baichwal which absorb water and form gels (column 8, lines 22-25) would not do so on contact with mucosal surfaces." The Office Action also complained on page 12 that Applicants' assertions regarding unexpectedly good results do "not compare the claimed invention with delivery of an antigen and another polysaccharide such as alginate or carrageenan."

Applicants respectfully reply that as discussed in paragraph 22 of Dr. Ni's Declaration, Baichwal does not actually assert anything relevant to *in-situ* gellation in Column 8 or anywhere else therein. As explained in Dr. Ni's Declaration, while the recited references allude to the well know fact that some polysaccharides are capable of forming gels under some conditions, none of the references cited in the Office Action, including Baichwal, Watts, or Ni, actually teach or suggest "*in-situ*" gellation of any of the compositions they disclose.

Applicants cannot currently present data that directly compare the *in-situ* gellation capabilities of their claimed pectin-containing solid powder compositions with similar solid powder compositions. Applicants have however disclosed, in their specification Example 8, comparative data on the *in-situ* gellation capabilities of Aloe Pectins, prior art pectins, and other polymers including alginates, in liquid "*in-situ* gelling" compositions. As disclosed in Applicants' Example 8, liquid formulations comprising Aloe pectins form high quality *in-situ* gels when subcutaneously injected, at concentrations as low as 0.1-0.25%. Prior art commercially available pectins having lower molecular weights and higher degrees of methylation gelled "*in-situ*" at higher concentrations (3.0-3.3 %). In contrast, liquid compositions comprising alginates at 0.5% did not form gels at all in *in-vitro*, *in-situ* gellation

assays, and only formed small amounts of smear-like substances when injected subcutaneously, indicating that most of the injected liquid alginate compositions, which would arguably be analogous to Baichwals' closest compositions, dissolved away without significant "*in-situ*" gellation. Accordingly, Applicants' data disclosed in Example 8 provides at least some data to indicate that pharmaceutical compositions comprising alginates, if they are capable of *in-situ* gellation at all, are markedly inferior compositions for *in-situ* gellation purposes, as compared to Applicants' claimed compositions comprising low methoxyl pectins, which readily form *in-situ* gels.

In view of the foregoing claim amendments and arguments, and the evidence of long felt and unmet needs in the art, and evidence of unexpectedly superior results provided in Dr. Ni's Declaration, the rejection of Applicants' claims for obviousness has been overcome.

CONCLUSION

Applicants respectfully submit that all outstanding objections and rejections stated in the Office Action have been overcome and should be withdrawn. Accordingly, the application is believed to be in condition for allowance and Applicants respectfully request issuance of a Notice of Allowance.

Attached herewith is a Request for a Two Month Extension of Time, Request for Continued Examination, and a Credit Card Payment Form PTO-2038 authorizing payment in the amount of $640.00, including $230.00 for the Two Month Extension of Time fee for a small entity under 37 C.F.R. § 1(a)(2), and $410.00 for a Request for Continued Examination for a small entity under 37 C.F.R. § 1.114. This amount is believed to be correct; however, the

Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as Express Mail No. EL 997679662 US in an envelope addressed to: MAIL STOP RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Christopher L. Curfman, Ph.D. **Date** October 31, 2007